California MEDICINE

For information on preparation of manuscript, see advertising page 2

EDITORIAL

Poliomyelitis Vaccination

SURGEON GENERAL SCHEELE and Associate Director of Laboratories* Shannon conclude their final report "The Public Health Implications in a Program of Vaccination Against Poliomyelitis"† with the statement: "Final decision on the use of vaccine remains the responsibility of individual physicians and health officers."

Millions of words have been written about the current experience with poliomyelitis vaccine. It has been said that not twenty men in the country could successfully negotiate all the ramifications of what actually happened. Few physicians are in a position to have complete knowledge of this entire affair but it is certainly necessary for them to study the facts and conclusions which have been presented in order to arrive at a decision which will guide them in discharging their responsibility for the administration of vaccine. Many theoretical conclusions must be decided by expert virologists but very many of the observations are entirely intelligible to the alert clinician.

The Francis evaluation of the field trials described a carefully planned scientific experiment on a fairly large scale. This report was completely reassuring in the matter of safety, it detailed a convincingly encouraging response in antibody production and supported the belief that a considerable degree of clinical protection was thus established, especially against the severer manifestations of poliomyelitis.

Transition to mass production of the vaccine, approval by the Public Health Service, and institution of nationwide administration were impetuously effected. There was little time or opportunity for examination of the field trial results by those with the ultimate responsibility of carrying out the authoritarian directive for mass immunization. Some protests were heard but many were silenced by the hope that we stood on the brink of an effective control measure for this serious problem. Difficulties which might have been anticipated were not foreseen. Physicians cannot lightly escape responsibility but voices once stilled cannot now be raised too loudly in protest.

Although the Francis Report promised complete safety of the vaccine, it was quickly discovered that under the conditions of routine application this assurance was not entirely borne out. Paralysis occasionally followed vaccination and the time interval of its appearance and localization to the injected extremity paralleled the experience of twenty years ago in which a crude vaccine later found to contain live virus was used on a small scale for similar purpose. A further disturbing development was the appearance of secondary cases of paralytic disease in the families of inoculated children.

These bad effects were most frequent with the product of a single manufacturer but were not encountered in all lots from this source prepared by identical methods nor even in any great number of children injected with the same lot of vaccine. Although most of these unpleasant incidents occurred with vaccine from this single source, other sequelae of persuasive similarity followed the use of vaccines produced by other manufacturers.

Early efforts to explain away these difficulties on the basis of pure chance, or from the use of vaccine during the incubation period of naturally acquired disease, or from the possible provocative effect of any injection in precipitating paralytic symptoms all quickly collapsed and almost every observer was soon convinced that these particular results could only be due to the persistence in the vaccine of some live virus which had escaped the killing effect of formalin.

The mass administration of vaccine was inadvertently a controlled experiment in which paralytic poliomyelitis occurred in numerous patients injected with some lots from one manufacturer, in occasional preparations from at least one other laboratory, and perhaps not at all from still other sources, the observed number of cases being sufficiently great to indicate that the sequelae were owing to essential differences in the vaccine preparations. One of the most convincing items of clinical evidence that live virus must have persisted in some of the preparations was that relatively so many children age one

*Of the National Institutes of Health.
†J.A.M.A., 158:1249, August 6, 1955.

to two years — during maximal susceptibility — should develop the disease following vaccination, the presence of live virus thus being demonstrated in a subject more sensitive than tissue culture or the laboratory monkey. The final bit of evidence was afforded by the isolation of live virus by Gebhardt from a lot of vaccine known to have been used for vaccination in a case in which paralysis followed injection.

A desperate effort was made to pin the responsibility to a single manufacturer—Cutter—but all of the vaccine produced followed carefully prescribed procedure. To date there has been no evidence introduced that there was any failure of conformance with established safety standards in the preparation of any of the suspect vaccine and it seems entirely likely that any discovered defect would have been quickly reported. The inescapable conclusion is that standard methods of production were in some way at fault and that inadvertent departure from these standards was not responsible for impaired safety.

The safety of some lots of vaccine as compared with those which caused trouble may have been due to slight modifications in procedure well within the framework of that laid down for the manufacturer. There was certainly some variation in the actual length of time during which the virus was exposed to formalin. Reportedly the formalin was not finally removed from one preparation which proved safe. Merthiolate was added as a preservative to the product of one manufacturer but when this addition was shown to interfere with the antigenicity of type I virus in the field trials, versine was added to overcome this interference. It has been suggested that the inclusion of Merthiolate was an unsuspected safety factor* whatever its effect on antigenicity. Still another commercial vaccine contained Phemerol, a quarternary ammonium compound not only bacteriostatic (perhaps virocidal) but also a dispersing agent which might afford increased safety through better dilution of occasional surviving live virus particles.

There are extant the opinions of many virologists that stimulation of antigenic response is afforded only by live virus and that the effectiveness of "killed" vaccine depends upon the persistence of at least a very little live virus. Dr. Salk's contribution to the contrary is almost unparalleled. Thus the safety of an effective vaccine as demonstrated in the field trials might depend upon extreme dilution and dispersion of a very few remaining live particles.

Safety requirements have now been severely revised and the assurance of harmlessness is now quite convincing. It remains to be proved that the antigenicity of present vaccine will equal the results reported in the field trials.

Many matters affecting the field trials still bear careful scrutiny:

1. It remains for experience to demonstrate that rise in serum antibodies invariably parallels clinical protection. This seems to be a reasonable assumption and is at least indicated by the field trials, but such a conclusion cannot be a product of pure logic and is arrived at only by the passage of time and continued observation.

2. In only a small number of the persons exposed to poliomyelitis does the disease spontaneously develop, and it is known that many acquire infection without ever showing signs of illness. It is not altogether improbable that those with maximal constitutional susceptibility may by the very ones least protected by vaccination.

3. The Francis Report indicated much less protection in children six years old or younger as the result of vaccination, with an improved response at older ages. It would thus appear that vaccine is far more effective as a booster than as an instrument for basic immunization.

There are many other considerations which one might enumerate and which merit—and will certainly receive—continued study. Live vaccines using avirulent viruses may prove to be the final answer, but for this almost endless research is required. It seems unfortunate that the proposal of Sabin, Enders, and others that avirulent type I virus be substituted for the Mahoney strain (thus being essentially nonparalytic even if surviving formalin treatment) was rejected in the interests of haste.

Mass immunization this year might better have been proposed as a continued experiment to extend the field trials of 1954 rather than being proposed *ex cathedra* as the accomplished method for universal protection. A considerable and sufficient proportion of the public could then have chosen to accept the uncertainties and even the unsuspected risks of a protective measure which offered reasonable promise of success and would then have been better prepared for some degree of disappointment. To the extent that vaccine was given within a restricted age group, controls would automatically be set up in adjoining age groups between which comparisons could be made. In California maximum incidence is from age four to six and comparisons with those vaccinated at age six to eight might afford data of great value.

Should vaccine now be given as it becomes available? Each physician must decide this question himself, for there is now enough information to justify conclusions one way or another. Vaccine need not be impatiently rejected; indeed it must not be, for the careful and scientific studies of our experience to date hold much promise of the eventual development of an innocuous and effective immunizing agent. There is now convincing evidence of the safety of present preparations. Final conclusions regarding antibody response, and clinical protection will be served by analysis of all accumulating experience. More than seven million children have been vaccinated in the United States this summer and an additional one million in Canada. Much can be learned from the results in these children. It is unlikely that the laborious pathway which has led to success in smallpox, diphtheria, tetanus and pertussis can be completely bypassed even by the use of modern calculating machines.

Such errors of judgment as have been made have occurred in all good faith, and some degree of failure should not be permitted to interfere with a cooperative effort of the public and the medical profession in a sincere attempt to solve this problem.

*Poliomyelitis Vaccine, Pediatrics, 15:788, June 1, 1955.